Safety Data Sheet

Cisplatin

Division of Safety
National Institutes
of Health

WARNING!

THIS COMPOUND IS ACUTELY TOXIC, CARCINOGENIC, EMBRYOTOXIC, AND MUTAGENIC. IT IS READILY ABSORBED BY VARIOUS BODY TISSUES THROUGH THE INTESTINAL TRACT. AVOID FORMATION AND BREATHING OF AEROSOLS.

LABORATORY OPERATIONS SHOULD BE CONDUCTED IN A FUME HOOD, GLOVE BOX, OR VENTILATED CABINET.

AVOID SKIN CONTACT: IF EXPOSED, WASH WITH SOAP AND COLD WATER. AVOID WASHING WITH SOLVENTS AND EXPOSURE TO UV LIGHT. AVOID RUBBING OF SKIN OR INCREASING ITS TEMPERATURE.

FOR EYE EXPOSURE, IRRIGATE IMMEDIATELY WITH LARGE AMOUNTS OF WATER. FOR INGESTION, INDUCE VOMITING. DRINK MILK OR WATER. REFER FOR GASTRIC LAVAGE. FOR INHALATION, REMOVE VICTIM PROMPTLY TO CLEAN AIR. ADMINISTER RESCUE BREATHING IF NECESSARY. REFER TO PHYSICIAN.

IN CASE OF LABORATORY SPILL, WEAR PROTECTIVE CLOTHING DURING CLEANUP. AVOID SKIN CONTACT OR BREATHING OF AEROSOLS. SEE CASTEGNARO ET AL. (1985) FOR DETAILS. DISPOSE OF WASTE SOLUTIONS AND MATERIALS APPROPRIATELY.

A. Background

Cisplatin is a yellow solid, slightly soluble in cold water and insoluble in most common solvents. It is toxic, mutagenic, embryotoxic, and carcinogenic in animals and toxic in humans, the prime target being the kidney. Cisplatin is a potent antineoplastic agent, used in the treatment (alone or in combination with radiotherapy and/or other antineoplastics) of testicular, ovarian,

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bladder, head, and neck carcinomas, melanomas, and leukemias. Its chief mode of action appears to be intrastrand crosslinking at two sites of a DNA molecule, and in this respect it resembles bifunctional alkylating agents.

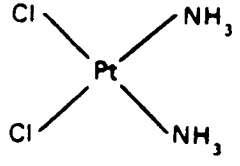
There are a great many review books and articles on cisplatin. Representative recent ones are: Prestayko et al., 1980; IARC, 198 Lippard, 1982; Douple, 1984; Hacker et al., 1984; Rosenberg, 1985; Riley and Sternson, 1985; Dagani, 1985.

. Chemical and Physical Data

1. Chemical Abstract No.: 15663-27-1

2. Synonyms: CDDP; DDP; cis-DDP; cis-diamminedichloroplatinum (II); cis-dichlorodiammineplatinum (II); cis-platinum (II); Cisplatyl; Platinex; Platinol; platinum, dichlorodiammine;[A] platinum, diamminedichloro-;[B] Platinum, diamminedichloro-, (SP 2);[C] NSC-119875; NCI-C55776.

3. Chemical structure and molecular weight



$Cl_2H_6N_2Pt$; 300.1

4. Density: No data.

5. Absorption spectroscopy: Ultraviolet and visible absorption maxima (ε) are: 203 (5,200), 301 (130), 362 (24.2). Mass and Raman (Riley and Sternson, 1985) and infrared (Clark and Williams, 1966) spectral data have been published.

6. Volatility: No data; may be assumed to be low.

7. Solubility: Water, 0.23; 0.9% NaCl, 0.15. Insoluble in most organic solvents except DMF (2%) and DMSO (35%) (All values in weight/volume.) (Riley and Sternson, 1985).

8. Description: Yellow odorless powder or crystals.

9. Boiling point: No data; melting point, 270°C with decomposition.

Chemical Abstracts name, used for listings in 7th Decennial Index.
Chemical Abstracts name, used for listings in 8th Decennial Index.
Chemical Abstracts name, used for listings in 9th Decennial Index and subsequently.

9. Stability: Solid cisplatin in pure form or as commercially prepared for parenteral injection (freeze-dried powder containing NaCl and mannitol) is stable, with a shelf life of 2 and 4 years at room temperature and under refrigeration, respectively. The stability of cisplatin in solutions is strongly dependent on the chloride concentration of such solutions; in the absence of chloride ion, cisplatin undergoes aquation (see B11 below), which is counteracted by chloride: there is less than 2% loss of cisplatin in 23 hours at room temperature if chloride concentration is equal to or more than 0.5% (Cheung et al., 1987). Greatest stability is found in presence of 0.9% NaCl. Addition of sodium bicarbonate to aqueous solutions of cisplatin increases its rate of disappearance. Other factors influencing stability are: cisplatin concentration, exposure to ultraviolet light (Greene et al., 1979; Hincal et al., 1979), and to aluminum and possibly stainless steel (Riley and Sternson, 1985). For stability in biological solutions (urine, plasma, etc.) see E1.

. Chemical reactivity: Aquation of cisplatin, a reaction in whic one or both chloride atoms are replaced by water molecules or (depending on pH) hydroxyl moieties, has been discussed in detail (Rosenberg, 1979). Cisplatin also reacts strongly with nucleophiles (bisulfite, methionine, nucleic acid constituents, and proteins) (Howe-Grant and Lippard, 1980). When allowed to "age" in injection solution (37°C, 12 months) cisplatin is converted to Platin B Salt ($NH_4[Pt(NH_3)Cl_3]$) and Magnus Red Double Salt ($[PtCl(NH)_3^+ + PtCl_3NH_3^-]$) (Peer and Litz, 1981).

. Flashpoint: No data.

. Autoignition temperature: No data.

. Explosive limits in air: No data.

ire, Explosion, and Reactivity Hazard Data

. Cisplatin does not require special fire-fighting procedures or equipment and does not present unusual fire and explosion hazards.

. The presence of alkali, ultraviolet light, or nucleophiles contributes to instability of cisplatin.

. Incompatibilities are contact with aluminum (formation of black precipitates) and possibly stainless steel.

. Cisplatin does not require non-spark equipment.

Operational Procedures

The NIH Guidelines for the Laboratory Use of Chemical Carcinogens describe operational practices to be followed when potentially carcinogenic chemicals are used in NIH laboratories. The NIH Guidelines should be consulted to identify the proper use conditions required and specific controls to be implemented during normal and complex operations or manipulations involving cisplatin.

It should be emphasized that this data sheet and the NIH Guidelines are intended as starting points for the implementation of good laboratory practices when using this compound. The practices and procedures described in the following sections pertain to the National Institutes of Health and may not be universally applicable to other institutions. Administrators and/or researchers at other institutions should modify the following items as needed to reflect their individual management system and current occupational and environmental regulations.

Solutions of cisplatin penetrate various glove materials (Laidlaw et al., 1984). This factor should be taken into account when handling cisplatin.

1. Chemical inactivation: Validated methods have been reported (Castegnaro et al., 1985).

2. Decontamination: Turn off equipment that could be affected by cisplatin or the materials used for cleanup. If there is any uncertainty regarding the procedures to be followed for decontamination, call the NIH Fire Department (dial 116) for assistance. Consult Castegnaro et al., 1985 for details concerning decontamination of surfaces, glassware, and animal cages.

3. Disposal: It may be possible to decontaminate waste streams containing cisplatin before disposal. For details, see Castegnaro et al., 1985. No waste streams containing cisplatin shall be disposed of in sinks or general refuse. Surplus cisplatin or chemical waste streams contaminated with cisplatin shall be handled as hazardous chemical waste and disposed of in accordance with the NIH chemical waste disposal system. Non-chemical waste (e.g., animal carcasses and bedding) containing cisplatin shall be handled and packaged for incineration in accordance with the NIH medical-pathological waste disposal system. Potentially infectious waste (e.g., tissue cultures) containing cisplatin shall be disinfected by heat using a standard autoclave treatment and packaged for incineration, as above. Burnable waste (e.g., absorbent bench top liners) minimally contaminated with cisplatin shall be handled as potentially infectious waste and packaged for incineration, as above. Absorbent materials (e.g., associated with spill cleanup) grossly contaminated shall be handled in accordance with the chemical waste disposal system. Radioactive waste containing cisplatin shall be handled in accordance with the NIH radioactive waste disposal system.

4. Storage: Store solid cisplatin in dark-colored, tightly closed containers, preferably under refrigeration. Avoid exposure to ultraviolet light and moisture. Store working quantities of cisplatin and its solutions in an explosion-safe refrigerator in the work area.

Monitoring and Measurement Procedures Including Direct Field Measurements and Sampling for Subsequent Laboratory Analysis

1. Sampling: No particular sampling precautions are necessary if the analytical objective is total platinum in biological samples. However, stringent precautions must be applied if free cisplatin is to be measured, because of the high reactivity of cisplatin with nucleophiles contained in tissue, plasma, and urine. Blood samples should be stored in an ice bath, centrifuged at 4°C within 30 minutes of collection, ultrafiltered, and stored at -20°C. Urine samples should be stored at -60°C (Drummer et al., 1984). Analysis (e.g., by high-pressure liquid chromatography) must be carried out within 72 hours even if these storage conditions are observed, and preferably as soon as possible (Riley and Sternson, 1985).

2. Analysis:
   a. Total platinum: The most widely used methods are based on atomic absorption spectrometry after digestion of samples with aqua regia or similar strong oxidants. The lower limit of detectability is 200 ng Pt/0.5 g of tissue (Pera and Harder, 1977; Bannister et al., 1978; Denniston et al., 1981).

   b. Specific analysis: Nearly all analytical methods involve high-pressure liquid chromatography, usually after derivatization with diethyl dithiocarbamate (Bannister et al., 1979; Andrews et al., 1984; Drummer et al., 1984), with a sensitivity of 50 ng per ml of urine or plasma ultrafiltrate. Post-column detection methods, when this derivatization is not used, include atomic absorption spectroscopy (Riley et al., 1982), ultraviolet absorption after reaction with sodium bisulfite (Sternson et al., 1983; Marsh et al., 1984), and polarography following oxidation and ethylene diamine complexation (Bartošek and Cattaneo, 1981; Bartošek et al., 1983).

Biological Effects (Animal and Human)

1. Absorption: There is little information. Cisplatin is usually administered parenterally (bolus injection or infusion) to animals or patients; there is no report regarding the use of oral administration. Lack of teratogenicity of cisplatin implies probable inability to pass the placental barrier (Köpf-Maier et al., 1985).

Distribution and pharmacokinetics: Most of the studies on distribution of cisplatin in the animal body have been carried out with the use of radiolabeled (^{195m}Pt) cisplatin and thus represent distribution of total platinum rather than the active drug. After intravenous injection plasma clearance is biphasic with half times of less than 1 hour and several days, respectively, in dogs (Litterst et al., 1976; Pretorius et al., 1981) and patients (Gormley et al., 1979; Ribaud et al., 1981). After intraperitoneal injection in dogs, serum peaks are reached in 5 minutes followed by similar biphasic decline (Pretorius et al., 1981). This is followed by distribution principally to kidney, liver, muscle and skin, gonads, spleen, and adrenals, with considerably prolonged retention in kidney, liver, and gonads (Litterst et al., 1976; Bénard et al., 1983). There is little detectable platinum in red blood cells, and little or no penetration of the blood-brain barrier (Gormley et al., 1981). Pharmacokinetic models have been developed for several species of animals and man (LeRoy et al., 1979; Farris et al., 1985; King et al., 1986). These models assume stability of cisplatin in plasma (because of high chloride concentration); intracellular conversion to aquated form(s) which are considered to be the toxicologically active species; and reaction with low molecular weight nucleophiles and nucleophilic sites on macromolecules.

Metabolism and excretion: The intracellular metabolism of cisplatin to active metabolites has been outlined above (F2) and reviewed (Rosenberg, 1979; Prestayko, 1980; Zwelling, 1986). The current thinking is that the activated form of cisplatin reacts with guanine residues of DNA to produce intrastrand and interstrand crosslinks, as well as with nucleophilic moieties o proteins; of these, the intrastrand DNA reaction is by far the most significant in terms of toxic (and antineoplastic) activit (Pinto and Lippard, 1985). It is interesting to note that the trans isomer of cisplatin, which has no antineoplastic activity but which also binds to chromosomal DNA, is rapidly excised by repair mechanism from DNA while the cisplatin adduct is not (Ciccarelli et al., 1985). Excretion of cisplatin is almost entirely via the kidney, with only minimal amounts appearing in the bile. While most of the urinary platinum is in the form of unreacted cisplatin (Safirstein et al., 1983), some metabolic derivatives have been separated by chromatography, and one of them tentatively identified as the methionine complex with cisplatin (Daley-Yates and McBrien, 1983).

Toxic effects: The acute LD50 in the mouse is 12-13 mg/kg iv and 17.8 mg/kg ip. When multiple doses are given, the LD50 is estimated to be 1.4 mg/kg/day in the mouse (ip, one to nine doses) and 1.25 mg/kg/day in the monkey (iv, five doses). Toxi effects in animals and man have been reviewed (Kovach et al., 1973; von Hoff et al., 1979; Prestayko, 1980). Major effects are on the kidney, resulting in tubular necrosis, dilation of

convoluted tubules, and formation of casts. In the contraindicate its usefulness in chemotherapy; however, the nephrotoxic effects can be prevented by vigorous hydration of patients before, during, and immediately following treatment, preferably with mannitol solutions (Krakoff, 1979; Porter and Bennett, 1981). Other toxic symptoms include nausea, vomiting, hemorrhagic enterocolitis, and leukopenia. Ototoxicity has been noted particularly in the guinea pig with complete and permanent loss of hearing (Fleischman et al., 1975) and less severely in man (von Hoff et al., 1979) and other species (Stadnicki et al., 1975), resulting from loss of hair cells in the organ of Corti. There is no obvious neurotoxicity except following intracarotid administration (Neuwelt et al., 1983).

5. Carcinogenic effects: These have been reviewed (IARC, 1981). Subsequent to the one study cited in this review, which reported significant increase in pulmonary adenomas in mice over controls, a similar study in rats showed 12 leukemias and one renal fibrosarcoma among the 33/50 deaths within 455 days, with no malignancies noted in controls (Kempf and Ivankovic, 1986).

6. Mutagenic and teratogenic effects: Cisplatin is mutagenic in the Ames test (without activation), but only in strains of S. typhimurium specific for base substitutions, and not in those specific for frame shift mutations (Rosenberg, 1979). This is to be expected on the basis of the intrastrand toxic reaction of cisplatin with DNA. It is also mutagenic to E. coli (Beck and Brubaker, 1975), and in a variety of animal cells in vitro (summarized in IARC, 1981). Embryotoxicity and some skeletal malformations in mice have been reported (Lazar et al., 1979) but on the whole, teratogenic effects appear to be no more frequent in experimental animals than in controls (Köpf-Maier et al., 1985).

Emergency Treatment

1. Skin and eye exposure: For skin exposure, remove contaminated clothing and wash skin with soap and water. Skin should not be rinsed with organic solvents or scanned with ultraviolet light. Avoid rubbing of skin or increasing its temperature. For eye exposure, irrigate immediately with sodium bicarbonate solution, followed by copious quantities of running water for at least 15 minutes. Obtain ophthalmological evaluation.

2. Ingestion: Drink plenty of water or milk. Induce vomiting. Refer for gastric lavage.

3. Inhalation: Remove victim promptly to clean air. Administer rescue breathing if necessary.

4. Refer to physician at once. Consider treatment for pulmonary irritation.

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